Supplementary Figure 1: Gene expression and cytokine production of *in vitro* generated Th22 cells.
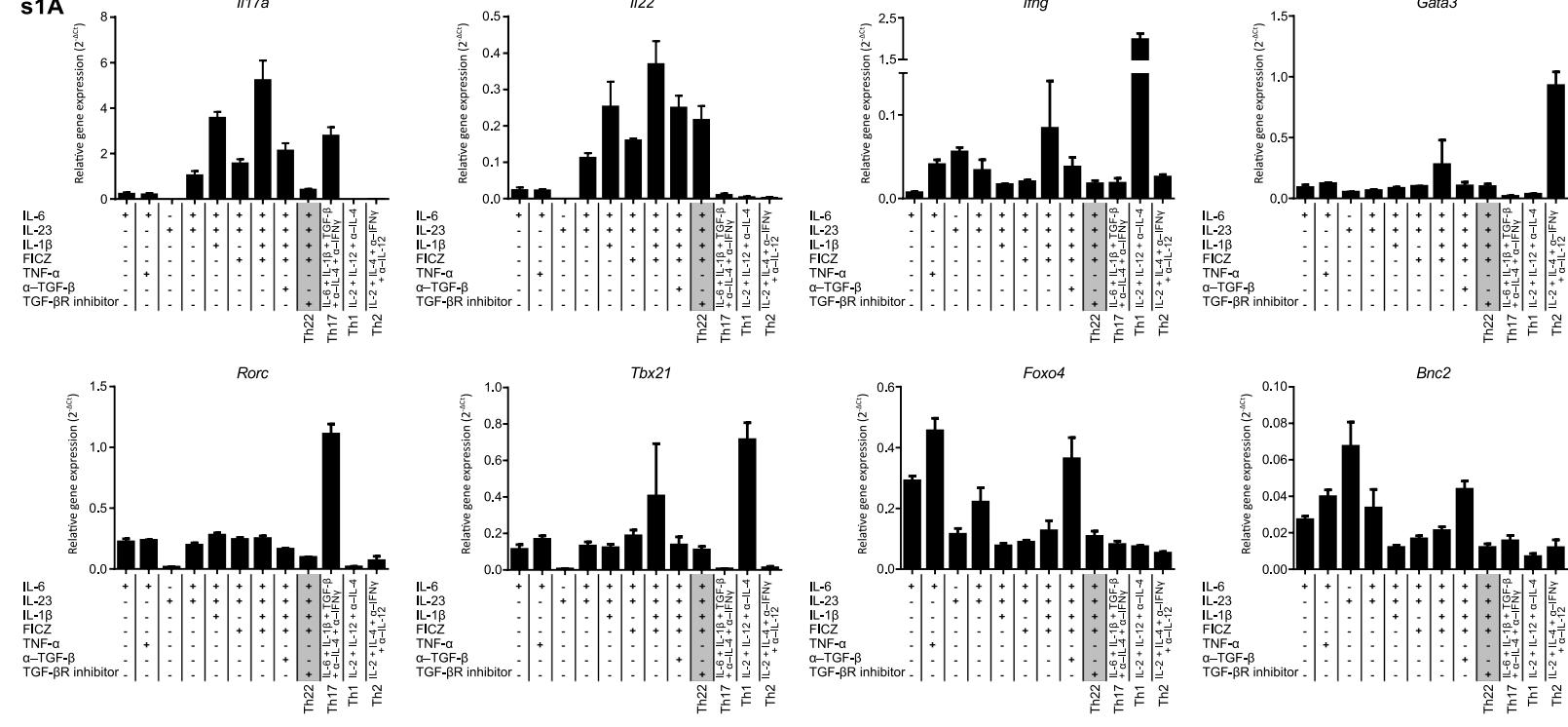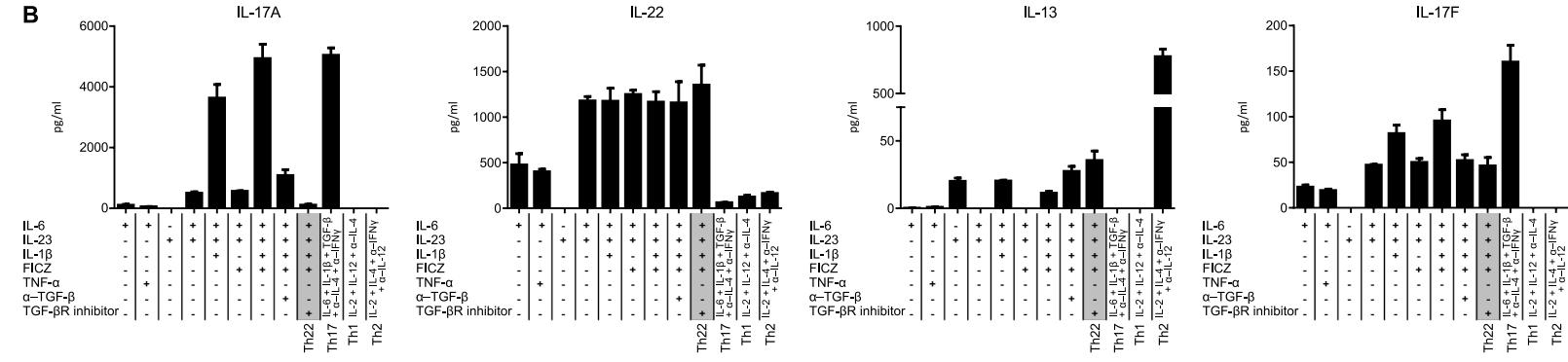
Gene expression of naïve Th cells differentiated for 3 days under varying polarizing conditions was determined for the gene indicated (A). Expression is normalized relative to the housekeeping gene *Hprt*. Cytokine levels in culture supernatant of naïve Th2 cells differentiated for 3 days under varying polarizing conditions was determined for IL-17A, IL-22, IL-13 and IL-17F (B). Error bars represent SEM (n=6 per group from 3 independent experiments).
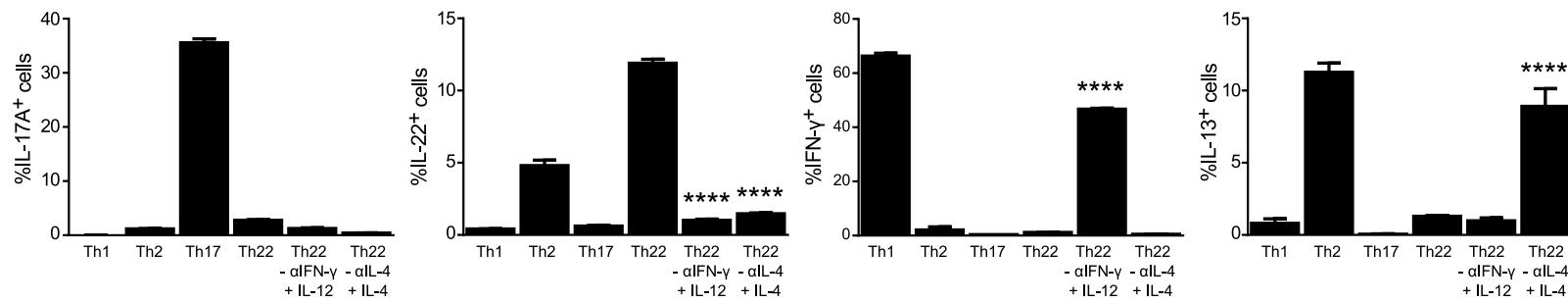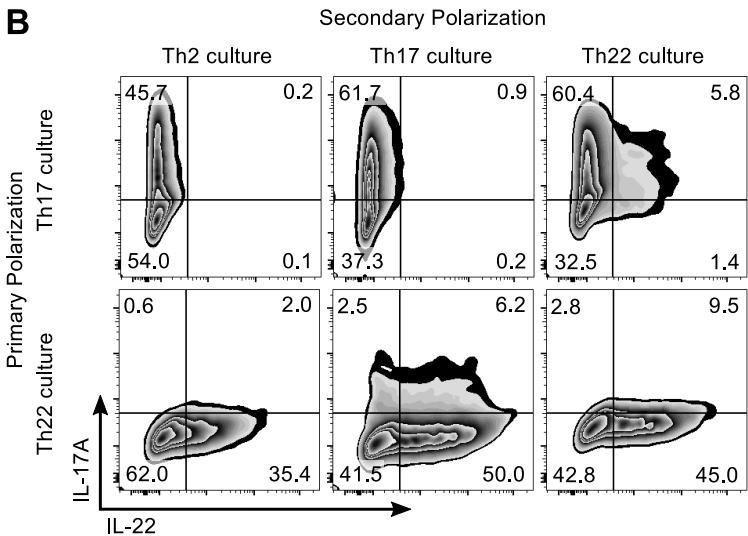
Supplementary Figure 2: IL-4 or IL-12 administration inhibits Th22 differentiation and sorted Th22 cells re-stimulated under Th2 conditions exhibit plasticity *in vitro*.
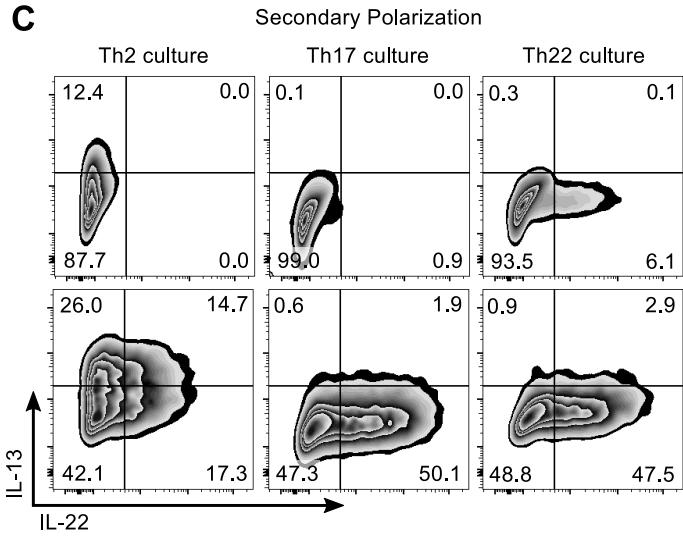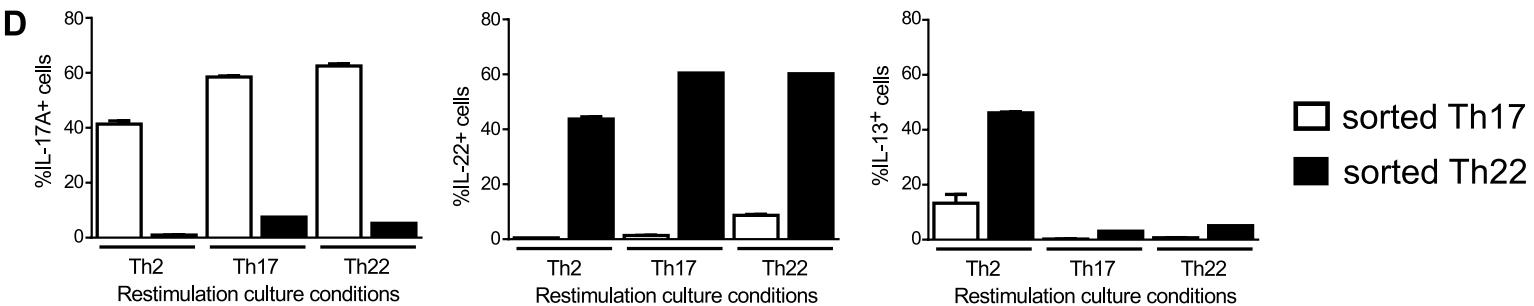
Naïve Th cells were cultured for 3 days under Th1, Th2, Th17 or Th22 conditions or under Th22 conditions with either rIL-12 (10ng/ml) lacking anti-IFN-γ or rIL-4 (20ng/ml) lacking anti-IL-4. Percentage of IL-17A+, IL-22+, IFN-γ+ and IL-13+ cells are graphed (A). Cultures of enriched Th17 and Th22 cells were generated from IL-17eGFP x IL-22tdTomato reporter mice, using optimal polarizing conditions for the first 3 days, and cells sorted for Th17 cells (CD4+CD44+IL-17eGFP+) or Th22 cells (CD4+CD44+IL-17eGFP-IL-22tdTomato+). Purified Th17 and Th22 cells were re-stimulated under Th2, Th17 and Th22 conditions for a further 3 days and the expression of IL-17A, IL-22 and IL-13 determined. Representative plots of IL-17eGFP, IL-22tdTomato and IL-13 expression in re-stimulated, fixed Th17 and Th22 cells are shown (B/C). Cell populations in FACS plots are pre-gated on CD4+CD44+ and viable cells. Quantification of IL-17A+, IL-22+ and IL-13+ cells in sorted Th17 and Th22 populations re-stimulated under Th2, Th17 and Th22 conditions (D). Error bars represent SEM (n=3 per group (A); 2 per group (D)).

Supplementary Table I: Differentially expressed transcripts between Th17 and Th22 cells. Gene transcription data generated using RNA isolated from sorted Th17 (CD4+CD44+IL-17eGFP+) and Th22 cells (CD4+CD44+IL-17eGFP-IL-22tdTomato+) quantified by mouse whole transcriptome microarray. All transcripts with >2-fold difference and p<0.05 are presented.

Transcripts upregulated in Th17 cells (vs. Th22 cells)				Transcripts upregulated in Th22 cells (vs. Th17 cells)			
Gene symbol	Transcript Cluster ID	Fold Change (Th17/Th22)	ANOVA p-value (Th17/Th22)	Gene symbol	Transcript Cluster ID	Fold Change (Th22/Th17)	ANOVA p-value (Th22/Th17)
Gpr15	17331212	15.90	0.000	Gzmb	17307033	38.14	0.000
Igkv6-23	17459423	15.41	0.000	Hamp	17489363	15.21	0.004
Nt5e	17520073	13.96	0.000	Il22	17237581	11.39	0.013
Klrd1	17463567	13.85	0.000	Il3	17262823	11.24	0.024
Il10	17216990	12.11	0.004	Ccl5	17266946	8.60	0.003
Ahr	17280729	11.78	0.002	Lum	17236811	8.39	0.002
Ccl20	17214857	8.55	0.030	*Akr1c18*	17290263	8.32	0.007
Gm15655	17505903	8.45	0.001	Trat1	17330805	8.13	0.004
Ly6g	17312219	8.19	0.041	Ms4a4b	17357659	8.07	0.002
Klre1	17463557	8.03	0.002	Gbp11	17450515	7.99	0.001
Serpinb1a	17291694	7.84	0.001	Xaf1	17252341	7.77	0.001
Maf	17513289	7.74	0.000	Tnip3	17459196	7.51	0.001
Klrc2	17471586	7.63	0.013	Trim30d	17494408	7.32	0.002
Il17a	17211369	7.22	0.013	*Akr1c13*	17284936	6.69	0.008
Igk-V21	17459421	7.20	0.001	Ifih1	17385797	6.29	0.001
Cldnd1	17326438	6.39	0.000	Il1r2	17212174	6.25	0.007
Art2a-ps	17493906	6.07	0.002	Mndal	17230067	5.90	0.008
Il9	17293013	5.93	0.013	Gm5483	17325329	5.58	0.019
Tmem176b	17466624	5.86	0.001	Nkg7	17477101	5.58	0.000
LOC102638993	17480924	5.76	0.002	Lilr4b	17233210	4.94	0.001
Ctla2b	17293348	5.60	0.001	Gzma	17296286	4.78	0.004
Il17f	17221627	5.53	0.007	Slc17a6	17478459	4.52	0.003
Pdpn	17432440	5.49	0.001	Ermn	17385398	4.45	0.015
Klrc1	17471598	5.34	0.003	Ifitm3	17497718	4.44	0.004
Gm22164	17308620	5.05	0.000	Serpinb6b	17286354	4.40	0.005
Myo3b	17371574	4.86	0.001	Gm5416	17325335	4.34	0.009
Cd86	17330203	4.83	0.004	Ifi44	17411147	4.27	0.008
Gm13994	17375587	4.78	0.003	Il13	17262695	4.14	0.004
Klrc3	17471578	4.76	0.031	Gbp8	17450434	4.13	0.009
Klri2	17471616	4.55	0.014	Plxnc1	17244439	3.99	0.000
Tmem176a	17458393	4.49	0.005	Epsti1	17302141	3.95	0.000
Aqp3	17424119	4.34	0.001	Ms4a4a	17357640	3.90	0.026
Dab2	17309935	4.32	0.006	Lilrb4a	17233226	3.84	0.001
Nipal1	17438062	4.25	0.003	Inhba	17285438	3.80	0.010
Lbp	17378827	4.08	0.001	Sox5os3	17464192	3.63	0.005
Ikzf3	17268820	4.03	0.001	Ms4a6d	17362973	3.51	0.014
Rbp1	17520624	3.92	0.016	Gbp9	17450448	3.48	0.000
Ctsw	17361605	3.76	0.000	Egfr	17247389	3.43	0.004
LOC102633880	17292026	3.74	0.000	Ebf1	17248691	3.41	0.004
Ust	17239102	3.71	0.000	Dgkk	17532755	3.37	0.003
Lgr4	17374098	3.67	0.002	Gbp4	17450461	3.37	0.002
Rb1	17308600	3.53	0.000	Nrn1	17291874	3.37	0.002
Alpk2	17355060	3.38	0.000	Phf11b	17307280	3.34	0.000
Ldlrad4	17351559	3.38	0.000	Tnfsf8	17426356	3.31	0.001
Cpox	17326428	3.31	0.000	Atf3	17231033	3.26	0.002
Myof	17364280	3.28	0.003	*AI504432*	17401530	3.24	0.002
Cpd	17266157	3.27	0.001	Gm29719	17340532	3.22	0.007
Sgk1	17232055	3.24	0.002	Batf3	17220787	3.19	0.005
Golm1	17293237	3.23	0.000	Mir155	17326794	3.17	0.017
Gm16033	17262050	3.22	0.005	Tigit	17330478	3.16	0.012
Cd101	17408470	3.21	0.000	Trim30a	17494394	3.15	0.004
H60b	17232102	3.17	0.024	*2010005H15Rik*	17325339	3.13	0.014
Il6st	17289889	3.15	0.004	St3gal1	17317675	3.13	0.001
Tfap2a	17292011	3.15	0.037	Gm12158	17262013	3.10	0.022
Aplp2	17525263	3.01	0.000	LOC73899	17360344	3.05	0.027

Gene	ID	Fold	p	Gene	ID	Fold	p
Prnp	17376541	3.00	0.007	Olfr60	17497641	3.05	0.013
Tmeff1	17414017	3.00	0.001	Sox5os2	17464187	3.05	0.026
Iyd	17231358	2.97	0.008	Coro2a	17425058	3.04	0.001
Ppp1r14c	17231349	2.95	0.005	Lrrk2	17314260	3.04	0.010
Gm15511	17528548	2.93	0.012	Casp1	17514424	3.02	0.003
Lpar6	17301886	2.92	0.001	Tnc	17426365	3.01	0.013
Art2b	17493912	2.88	0.028	Gstt1	17241934	3.00	0.002
Sema6d	17375557	2.84	0.001	Arhgef3	17298041	2.93	0.001
Adam19	17248754	2.71	0.000	Gm15135	17494322	2.93	0.002
Paqr8	17211375	2.61	0.001	Pparg	17461942	2.92	0.000
Gm22836	17529227	2.59	0.014	Tnp2	17328107	2.92	0.001
LOC105247442	17222066	2.53	0.003	Cd226	17352330	2.87	0.000
A630023P12Rik	17440530	2.50	0.009	Trim34b	17481284	2.84	0.000
Gm26065	17540497	2.49	0.014	Il18	17517105	2.82	0.007
Kynu	17370527	2.48	0.002	Ddx60	17501440	2.80	0.023
Peli2	17299401	2.48	0.001	Isg15	17434023	2.80	0.014
Acvr2a	17370598	2.46	0.001	Fam71b	17248793	2.78	0.009
Zfp318	17338087	2.46	0.000	Usp18	17462437	2.78	0.013
Crybg3	17331284	2.43	0.000	Calcrl	17387385	2.76	0.002
Emp1	17463781	2.43	0.004	Il33	17358598	2.76	0.036
Kctd12	17309154	2.43	0.008	Stfa1	17325347	2.76	0.019
Cd38	17437213	2.41	0.002	H2-Q8	17337122	2.74	0.004
Dst	17211587	2.36	0.000	Mnda	17230078	2.74	0.001
Gm23722	17222566	2.33	0.000	Slfn1	17254171	2.72	0.005
Tspan2	17401072	2.32	0.002	Tm6sf1	17479736	2.72	0.007
Txk	17448693	2.32	0.001	Coch	17275378	2.71	0.012
4930486L24Rik	17293338	2.30	0.024	Cd274	17358544	2.70	0.003
Cxcr6	17523642	2.29	0.003	Serpine2	17224771	2.70	0.037
Bcl6	17329433	2.28	0.001	Crtam	17525856	2.68	0.010
Ccr6	17333066	2.28	0.020	Gm11998	17247332	2.67	0.002
Pls1	17529764	2.26	0.021	Clec2i	17463454	2.66	0.028
Klrk1	17471565	2.25	0.005	Dcn	17236800	2.66	0.019
Gm17305	17251639	2.21	0.001	Trim34a	17481274	2.65	0.000
Slc4a4	17438832	2.21	0.000	Mocos	17349016	2.64	0.002
Vip	17231482	2.19	0.020	Sox5	17472641	2.64	0.003
Gm12205	17262586	2.18	0.017	*A630091E08Rik*	17493578	2.63	0.008
Gm25494	17238636	2.18	0.017	Mir31	17427131	2.63	0.032
Igf1r	17479099	2.18	0.003	Pyhin1	17219662	2.61	0.049
Lrig1	17469217	2.18	0.006	Crim1	17339801	2.58	0.002
Pramef25	17432496	2.18	0.005	Tespa1	17238705	2.58	0.002
Gm24650	17424161	2.16	0.002	Dock10	17224813	2.57	0.001
Gm8465	17333076	2.15	0.010	Gstt3	17241921	2.57	0.001
Acpp	17530406	2.14	0.005	Sox5os5	17464201	2.57	0.002
Epb41l2	17232283	2.14	0.001	*2610528A11Rik*	17305163	2.54	0.000
Gm23864	17344434	2.14	0.020	Tmem45a	17331078	2.54	0.001
Cyp1b1	17347448	2.13	0.014	Gnal	17351426	2.53	0.006
Zak	17371912	2.13	0.000	Sytl3	17332932	2.53	0.007
Olfr1445	17357891	2.10	0.033	Ifi27	17278200	2.52	0.001
Gfpt2	17249036	2.09	0.018	Olfr266	17408970	2.52	0.000
Gm25628	17311905	2.09	0.043	LOC102633032	17404291	2.50	0.017
Gsap	17435055	2.09	0.024	Snx9	17332783	2.50	0.001
Dnm3	17228906	2.08	0.018	Atp8b4	17391056	2.49	0.010
Gm11454	17379224	2.08	0.034	Ntrk3	17492244	2.49	0.002
Kctd14	17480349	2.07	0.006	Il1rl2	17212199	2.48	0.000
Procr	17378440	2.07	0.030	Isg20	17479317	2.47	0.011
Scpep1	17267601	2.07	0.001	LOC102634350	17464184	2.41	0.017
Dyrk4	17471179	2.04	0.019	Slc39a6	17353153	2.41	0.000
Myo1f	17336114	2.03	0.035	Rab19	17457504	2.40	0.006
Bmpr2	17213336	2.02	0.005	Cdh17	17411848	2.39	0.004
C920009B18Rik	17232112	2.02	0.001	*4833419F23Rik*	17348121	2.37	0.002

Casp4	17514435	2.37	0.010
Gm19705	17217825	2.37	0.000
H2-DMb2	17336414	2.37	0.022
5430427O19Rik	17536191	2.36	0.033
Ifitm2	17497713	2.36	0.021
Ido1	17508188	2.35	0.000
Samd9l	17464534	2.35	0.037
Kcna3	17401526	2.33	0.015
Gm28053	17458377	2.32	0.018
Tnfsf4	17218701	2.31	0.025
Trim12a	17494353	2.30	0.008
Gm26742	17350681	2.29	0.015
Gramd1b	17525803	2.28	0.000
Casp3	17501041	2.26	0.009
Rnf19b	17418916	2.25	0.002
Anxa1	17363407	2.24	0.003
E430016F16Rik	17492268	2.24	0.020
Gm14718	17535045	2.24	0.005
Gm16277	17360728	2.24	0.026
Oas1a	17452126	2.24	0.043
Gca	17371201	2.23	0.038
Gm19261	17362970	2.23	0.001
Zfp608	17354411	2.23	0.001
C430002N11Rik	17520582	2.22	0.003
Penk	17423030	2.20	0.004
Gbp7	17403224	2.19	0.006
Prkca	17271168	2.19	0.002
Peak1os	17517573	2.17	0.011
Trim12c	17494325	2.16	0.008
Cth	17411420	2.15	0.019
Il12rb2	17467323	2.15	0.000
Capsl	17310250	2.14	0.006
Gzmc	17307025	2.14	0.018
Cd80	17325608	2.13	0.014
Fah	17493005	2.13	0.007
Fhl2	17222642	2.13	0.004
Rasgrp1	17389647	2.13	0.000
Ckmt1	17375257	2.10	0.000
Clcn5	17539797	2.10	0.037
Oas1b	17441759	2.10	0.006
Peak1	17527433	2.10	0.001
B3gnt5	17323828	2.09	0.007
Nkain1	17430645	2.09	0.038
Gpr141	17290894	2.08	0.023
Lrp1	17245923	2.08	0.006
Man1a	17240880	2.08	0.001
Abcg3	17450414	2.07	0.003
Fasl	17228864	2.06	0.007
Insl6	17363790	2.06	0.021
Asah2	17363927	2.05	0.005
Gm6904	17307260	2.05	0.044
Il15ra	17367004	2.05	0.039
Fam171b	17372552	2.03	0.006
Gpm6b	17539611	2.03	0.045
Ephx1	17230484	2.02	0.000
Sik3	17516871	2.01	0.001
Slamf1	17219407	2.01	0.000

Supplementary Table II: **Differential gene expression of predicted secreted transcripts from Th17 and Th22 cells.** Secretome prediction was performed using SignalPv4.1 and TargetPv1.1 analysis, to identify secreted products differentially expressed between Th17 and Th22 cells in the microarray dataset. A probability cut-off value of 0.8 was used for secretome prediction. All genes with >2-fold difference and $p<0.05$ are presented.

Transcripts of predicted secreted proteins of Th17 cells			Transcripts of predicted secreted proteins of Th22 cells		
Gene Symbol	Fold Change (Th17/Th22)	ANOVA p-value (Th17/Th22)	Gene Symbol	Fold Change (Th22/Th17)	ANOVA p-value (Th22/Th17)
Nt5e	13.96	0.000	Gzmb	38.14	0.000
Il10	12.11	0.004	Hamp	15.21	0.004
Ccl20	8.55	0.030	Il22	11.39	0.013
Il17a	7.22	0.013	Il3	11.24	0.024
Il9	5.93	0.013	Ccl5	8.60	0.003
Il17f	5.53	0.007	Lum	8.39	0.002
Lbp	4.08	0.001	Il1r2	6.25	0.007
Ctsw	3.76	0.000	Lilr4b	4.94	0.001
H60b	3.17	0.024	Gzma	4.78	0.004
Il6st	3.15	0.004	Il13	4.14	0.004
Art2b	2.88	0.028	Lilrb4a	3.84	0.001
Sema6d	2.84	0.001	Inhba	3.80	0.010
Adam19	2.71	0.000	Cd226	2.87	0.000
Vip	2.19	0.020	H2-Q8	2.74	0.004
Igf1r	2.18	0.003	Coch	2.71	0.012
Lrig1	2.18	0.006	Cd274	2.70	0.003
Acpp	2.14	0.005	Crtam	2.68	0.010
Procr	2.07	0.030	Dcn	2.66	0.019
Scpep1	2.07	0.001	Crim1	2.58	0.002
Bmpr2	2.02	0.005	2610528A11Rik	2.54	0.000
			Ntrk3	2.49	0.002
			Cdh17	2.39	0.004
			H2-DMb2	2.37	0.022
			Penk	2.20	0.004
			Il12rb2	2.15	0.000
			Gzmc	2.14	0.018
			Lrp1	2.08	0.006
			Il15ra	2.05	0.039